

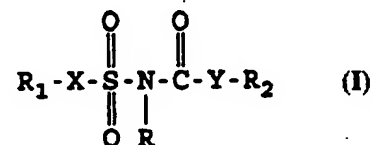
PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | | |
|---|--|---|---|
| (51) International Patent Classification ⁵ : C07C 307/02, 311/51, A61K 31/18, 31/325 | | A1 | (11) International Publication Number: WO 94/26702 (43) International Publication Date: 24 November 1994 (24.11.94) |
| (21) International Application Number: PCT/US94/05233 (22) International Filing Date: 11 May 1994 (11.05.94) (30) Priority Data: 08/062,515 14 May 1993 (14.05.93) US 08/223,932 13 April 1994 (13.04.94) US (71) Applicant: WARNER-LAMBERT COMPANY [US/US]; 2800 Plymouth Road, Ann Arbor, MI 48105 (US). (72) Inventors: LEE, Helen, Tsenwhei; 3625 Fox Hunt, Ann Arbor, MI 48105 (US). PICARD, Joseph, Armand; 5764 Princeton Place, Ypsilanti, MI 48197 (US). SLISKOVIC, Drago, Robert; 4860 Cole Boulevard, Ypsilanti, MI 48197 (US). WIERENGA, Wendell; 1968 Woodlily Court, Ann Arbor, MI 48103 (US). (74) Agents: ANDERSON, Elizabeth, M.; Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, MI 48105 (US) et al. | | (81) Designated States: AU, CA, CZ, FI, HU, JP, KR, NO, NZ, RU, SK, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> | |
| (54) Title: N-ACYL SULFAMIC ACID ESTERS (OR THIOESTERS), N-ACYL SULFONAMIDES, AND N-SULFONYL CARBAMIC ACID ESTERS (OR THIOESTERS) AS HYPERCHOLESTEROLEMIC AGENTS | | | |
| (57) Abstract The present invention is directed to compounds useful for the regulation of cholesterol of formula (I), methods for using them and pharmaceutical compositions thereof. In Formula (I) X and Y are oxygen, sulfur, or (CR'R") _n wherein n is 1 to 4; R is hydrogen, alkyl, or benzyl; R ₁ and R ₂ are phenyl, substituted phenyl, naphthyl, substituted naphthyl, an aralkyl group, an alkyl chain, adamantyl, or a cycloalkyl group. | | | |



-25-

2,6-diisopropylphenylacetyl chloride was replaced with adamantaneacetyl chloride;

^1H NMR(CDCl_3): 1.21 (d, 12H), 1.6-2.0 (m, 15H), 2.15 (s, 2H), 3.4 (m, 2H), 7.15-7.25 (m, 3H) ppm.

5

EXAMPLE 5

Synthesis of Sulfamic acid[[2,4,6-tris(1-methylethyl)-phenyllacetyl]-2,6-bis(1-methylethyl)phenyl ester

(a) 2,4,6-Triisopropylbenzyl alcohol

10 A solution of commercially available 2,4,6-triisopropylbenzoyl chloride (35 g, 131.2 mmol) in 400 mL ether was added slowly to a suspension of lithium aluminum hydride (LAH) (4.89 g, 131.2 mmol) in ether (300 mL) at -15°C . The mixture was slowly warmed to
15 room temperature over 18 hours. Saturated Na_2SO_4 solution was added slowly and the ether layer was separated, dried over MgSO_4 , and evaporated to dryness. The compound was used in the next step without further purification;

20 NMR (CDCl_3): δ 1.2-1.4 (m, 18H), 2.8-3.0 (m, 1H), 3.3-3.5 (m, 2H), 4.8 (s, 2H), 7.1 (s, 2H) ppm.

(b) 2,4,6-Triisopropylbenzyl bromide

25 A solution of PBr_3 (2.7 g, 10 mmol) in ether (10 mL) was added slowly to a solution of 2,4,6-triisopropylbenzyl alcohol (4.68 g, 20 mmol) in 20 mL of ether at room temperature. The mixture was stirred for 1 hour, 5 mL of absolute EtOH was added, and stirring was continued for another 0.5 hour. The solvent was
30 removed and the residue distributed between EtOAc and saturated Na_2CO_3 . The EtOAc layer was separated, washed with brine, and dried over MgSO_4 . The solvent was evaporated and the pure product was isolated by column chromatography (100% CH_2Cl_2 , 3.5 g, 59%);
35 NMR (CDCl_3): δ 1.2-1.4 (m, 18H), 2.8-3.0 (m, 1H), 3.2-3.45 (m, 2H), 4.7 (s, 2H), 7.04 (s, 2H) ppm.

-26-

(c) Sulfamic acid[2,4,6-tris(1-methylethyl)phenyll-acetyl]-2,6-bis(1-methylethyl)phenyl ester

A solution of 2,4,6-triisopropylbenzyl bromide (12 g, 40.4 mmol) in dry THF (160 mL) was added to a suspension of Mg powder (1.96 g, 80.8 mmol) (4 hours) in THF (20 mL) heated under reflux. 2,6-Diisopropylphenoxysulfonyl isocyanate (ROSO₂NCO) (see Phos. and Sulf., 19:167 (1984) for preparation) (11.45 g, 40.4 mmol) was added neat, and after the addition was completed, the reflux was continued for another 2 hours. The reaction was stirred at room temperature for 16 hours. Saturated NH₄Cl and EtOAc were added. The EtOAc layer was separated, dried over MgSO₄, filtered, and evaporated to dryness. After purification by column chromatography (4:1 hexane:EtOAc), the compound was isolated as white solid (13.5 g, 67%), mp 178-180°C.

EXAMPLE 6

20 Synthesis of sulfamic acid[[2,4,6-tris(1-methylethyl)-phenyllacetyl]-2,6-bis(1-methylethyl)phenyl ester sodium salt

This compound was prepared in the same manner as for the title compound of Example 2, except that the title compound of Example 1 was replaced with the title compound of Example 5, mp 250-252°C.

EXAMPLE 7

30 Synthesis of sulfamic acid(phenylacetyl)-2,6-bis-(1-methylethyl)phenyl ester

This compound was prepared in the same manner as the title compound of Example 5, except that 2,4,6-triisopropylbenzyl magnesium bromide was replaced with benzylmagnesium chloride (commercially available), mp 150-152°C.